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Epidemiologic Evidence for the Increased Cell Proliferation Model of Carcinogenesis

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Recent advances in the molecular genetics of cancer have provided a molecular basis for the concept that cell division is essential in the genesis of human cancer. The activation of oncogenes and inactivation of tumor-suppressor genes allows cancer development. The activation of oncogenes, whether by mutation, translocation, or amplification, requires cell division. Genetic errors that precede the development of a fully malignant tumor also include the loss of inactivation during mitosis of several tumor-suppressor genes that function to control normal cellular behavior (*1–3*). Most of the models currently favored suggest that the first hit is the inactivation by a mutational event of one of the two alleles of a tumor-supressor gene present in diploid cells, followed by a reduction to homozygosity of the faulty chromosome (*4*). The initial mutagenic event and the loss of the wild-type allele of the tumor-suppressor gene both require cell division. Thus, for expression of the full malignant phenotype, cells are absolutely required to divide.

Epidemiologic evidence indicates that increased cell proliferation induced by external or internal stimulation is indeed a common denominator in the pathogenesis of many human cancers. "Increased" may imply division of a subset of cells that would ordinarily not be dividing or increased mitotic activity above the baseline rate. The amount of irreparable DNA damage is a function of the level of cell division. Rapid cell division may "fix" DNA-damaging events by not allowing enough time for normal repair. Cells that would ordinarily not be replicating (e.g., the Schwann cells in the nerve sheath) may at times be stimulated to divide, and when this happens, tumors (e.g., schwannomas) may develop. Nondividing cells in adults, such as nerve cells and cardiomyocytes, never develop tumors.

Cell division increases the risk of errors of various kinds (*5*). Mutation is more likely to occur in a dividing cell because single-stranded DNA is more sensitive to damaging effects than double-stranded DNA. Cell division also allows mitotic recombination (e.g., nondisjunction, gene conversion), which results in changes more profound than those from a single mutation. Gene duplication that occurs during cell division may cause expression of previously unexpressed oncogenes. Cell division may also involve conversion of adducts to gaps or mutations.

Agents that may lead to increased cell proliferation and eventual neoplastic transformation include a wide variety of physical, infectious, and chemical agents (Tables 1 and 2). The cell proliferation factors listed in Table 1 are those whose primary carcinogenic action is to stimulate cell division. Those shown in Table 2 also seem likely to contribute to neoplasia by stimulating

Table 1. Human cancers associated with agents whose major action is induction of increased cell proliferation.

Factors causing cell proliferation	Cancer site
Hormones	
Estrogen	Endometrium
Estrogen and progesterone	Breast
Ovulation	Ovary
Drugs	
Oral contraceptives, anabolic steroids	Liver
Infectious agents	
Hepatitis B virus	Liver
Schistosoma hematobium	Bladder
Schistosoma japonicum	Colon
Clonorchis sinensis, *Opisthorchis viverrini*	Biliary tract
Tuberculosis	Lung
Epstein-Barr virus	Burkitt's lymphoma
Chemical agents	
Betel nut, lime	Oral cavity
Physical or mechanical trauma	
Asbestos	Mesothelial tissue, lung
Other chronic irritations	
Tropical ulcers	Skin

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Table 2. Human cancers probably associated with increased proliferation.

Factors causing cell proliferation	Cancer site
Hormones	
Testosterone	Prostate
Drugs	
Diuretics, analgesics	Kidney
Chemical agents	
Bile and pancreatic juice	Small intestine
Animal fat	Colon
Salt	Stomach
Tobacco	Oral cavity, lung, larynx
Physical or mechanical trauma	
Hard foods (e.g., coarsely ground corn)	Stomach
Gallstones	Gall bladder
Loud noise	Acoustic nerve
Head injury	Intracranial meninges
Other chronic irritations	
Reverse smoking	Hard palate
Chronic ulcerative colitis	Colon

cell division, but evidence that the mechanism listed is the one critical to carcinogenesis is weaker. Other agents, including such established carcinogens as tobacco, may exert their effects partly through increasing cell division. Examples of human cancers have been associated with increased cell proliferation caused by hormones, drugs, infectious agents, chemical agents, physical or mechanical traumas, and other chronic irritations. A fuller account of the role of increased cell division in human cancer has been published (*6*).

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